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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/715,036	11/20/2000	Hortense W. Dodo	077281-0104	6841

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EXAMINER

GIBBS, TERRA C

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 11/06/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.		Applicant(s)	
	09/715,036		DODO ET AL.	
	Examiner		Art Unit	
	Terra C. Gibbs		1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 1-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>9 and 8</u> | 6) <input type="checkbox"/> Other: _____ |

(#8 in part)

DETAILED ACTION

This Office Action is a response to the Application filed November 20, 2000 and the Response to Restriction Requirement filed August 8, 2002, Paper No. 10.

Claim 21 is pending in the instant application.

Claims 1-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

Claim 21 has been examined as indicated below.

Election/Restrictions

Applicant's election with traverse of Group V (claim 21) in Paper No. 12 is acknowledged. The traversal is on the ground(s) that the claims of Groups I and V are related to a method for producing a transgenic peanut plant with reduced or undetectable allergen protein content using a DNA comprising a peanut allergen gene including *Ara h* allergen gene or a homologous region common to more than one *Ara h* allergen gene. Additionally, Applicant argues that when searching for a homologous region common to more than one *Ara h* allergen gene, this search will encompass all *Ara h* allergen genes that are covered by claims of Group I. Further, Applicant argues that searching and examining all of the claims of Groups I and V would not place an undue burden on the examiner. This is not found persuasive because, as argued in the restriction requirement (Paper No. 10), "Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another".

Furthermore, "Each nucleotide sequence is presumed to represent an independent and distinct invention"... "It has been determined that one sequence constitutes a reasonable number for examination purposes". Therefore, a search for more than one DNA comprising a peanut *Ara h* allergen gene will represent an undue burden on the Patent and Trademark Office.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

The information disclosure statement filed September 18, 2001, in Paper No. 8 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Only publications A1-A16 of the information disclosure statement were contained in the application as filed. Applicant is asked to resubmit a legible copy of publications A17-A97 of the information disclosure statement, filed in Paper No. 8. Currently, only publications A1-A16 have been considered.

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 21 is drawn to a method for producing a transgenic peanut plant with reduced or undetectable allergen protein content in the seed, comprising identifying a homologous region common to more than one *Ara h* allergen gene; cloning the homologous region in a vector modified for peanut transformation; transforming a recipient peanut plant cell with the vector; and identifying a transgenic plant that produces seeds having reduced or undetectable allergen protein content. The specification, at page 18, lines 13-17 recite, "Peanut plants may be transformed with more than one peanut allergen antisense gene, and/or sense gene, and/or combined antisense and sense genes, or fragments of each gene, in order to produce peanut plants and seeds containing reduced or undetectable quantities of several different peanut allergen proteins". Given the broadest interpretation, the claim encompasses antisense gene expression and co-suppression.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed. This determination is based on several factors which, when considered together, illustrates that the art

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antisense technology in crops such as peanut plants is highly unpredictable. The discussion is also based on references whose teachings show that, despite a tremendous amount of experimentation by highly skilled artisans in the field of plant genetic engineering, there remain significant hurdles known in the art to make and/or use the invention over the scope claimed.

- (1) the nature of the invention;
- (2) the state of the prior art and the predictability or unpredictability of the art;
- (3) the amount of direction or guidance and the presence or absence of working examples;
- (4) the breadth of the claims; and
- (5) the quantity of experimentation required

(1) The nature of the invention. Methods of targeting nucleic acids into crop cells falls into the broad area known as genetic modification. While genetic modification is not a new technology, the ability to down regulate gene expression using antisense in plants is in its infancy. The technology of antisense delivery shares many of the obstacles recognized in actual therapy methods because successful therapy methods are, for the most part, based on the ability to deliver exogenous nucleic acids to cells or tissues of interest.

(2) The state of the prior art and the predictability or unpredictability of the art. The instant specification, at page 27, lines 4-10 disclose, "Antisense technology, however, has not been applied to peanut. Prior to the invention, there has not been peanut plants or germplasm, whether naturally occurring or genetically engineered, that is partially or completely allergen free. In fact, in an ELISA screen of 32 commercial peanut cultivars by the inventors of the instant invention, no allergen-free cultivars was identified, although a significant different in allergen level was found among the cultivars".

Shewry et al. (Journal of Chromatography, 2001 Vol. 756:327-335) assert, "Current technology allows gene expression to be down-regulated using antisense or co-suppression and

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future developments may allow targeted gene mutation or gene replacement. However, the application of this technology may be limited at least in the short term by the presence of multiple allergens and their contribution to food processing or other properties. Furthermore, the long-term stability of these systems needs to be established as reversion could have serious consequences” (see Abstract).

Metcalf et al. (Critical Reviews in Food Science and Nutrition, 1996 Vol. 36:165-186) assert, “Genetic engineering can also provide an important tool to reduce the levels of specific allergenic proteins in the food supply”... “the presence of multiple allergens in foods like peanuts and soybeans, however, greatly complicates this challenge. Furthermore, a protein that is an allergen and which also serves a critical structural or functional role cannot be removed without a negative impact on the plant” (see pages 180 and 181, last and paragraphs, respectively).

The unpredictability of the art of antisense in general further adds to the lack of enablement for the current invention. For example, Branch (TIBS, February 1998 Vol. 23, pages 45-50) addresses the unpredictability and the problems faced in the antisense art with the following statements: “Antisense molecules and ribozymes capture the imagination with their promise of rational drug design and exquisite specificity, however, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven.”; The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules.”; “Years of investigation can be required to figure out what an ‘antisense’ molecule is actually doing”.

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Assertions such as those from Shewry et al., Metcalfe et al. and Branch, in addition to self-admissions from the instant application appear to indicate that the state of the art of plant genetic engineering is unpredictable and those highly skilled in the art are working towards making the art of plant genetic engineering more predictable, but have many obstacles to overcome.

(3) The amount of direction or guidance and the presence or absence of working examples.

Applicants have not provided guidance in the specification toward a method for producing a transgenic peanut plant with reduced or undetectable allergen protein content in the seed.

The specification discloses the sequence homology amplified regions of *Ara* h1, h2, h3 and h5 allergen cDNAs cloned in sense and antisense orientations in transforming vectors. The specification fails to teach the successful delivery of sense and antisense transforming vectors in peanut plants. One skilled in the art would not accept on its face the examples given in the specification of sequence homology amplified regions of *Ara* h1, h2, h3 and h5 allergen cDNAs cloned in sense and antisense orientations in transforming vectors as being correlative or representative of regeneration of a transgenic peanut plant having reduced or undetectable allergen protein content in view of the lack of guidance in the specification and known unpredictability associated with the technology of plant genetic engineering and antisense, as cited in the references of Shewry et al., Metcalfe et al. and Branch, as discussed above. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with plant genetic engineering and antisense treatment.

(4-5) The breadth of the claims and the quantity of experimentation required. The current specification does not provide such guidance and one of ordinary skill in the art would be

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required to perform undue trial and error experimentation to practice the current invention. In order to practice the invention over the scope claimed, it would require trial and error or undue experimentation beyond which is taught in the specification to practice the invention drawn to a method for producing a transgenic peanut plant with reduced or undetectable allergen protein content in the seed. The quantity of undue experimentation required to practice the invention as claimed would include determining the presence of multiple allergens and their contribution to food processing or other properties, the long-term stability of gene suppression and overcoming the obstacle to routine antisense treatment, as exemplified in the references discussed above. Since the specification fails to provide any particular guidance for the production of a transgenic peanut plant with reduced or undetectable allergen protein content in the seed or successful delivery of antisense transformation vectors to peanut plants, where such antisense technology is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

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evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tada et al. (FEBS Letters, 1996 Vol. 391:341-345) in further view of Kleber-Janke et al. (Allergy and Immunology, 1999 Vol. 119:265-274) and Shewry et al. (Journal of Chromatography, 2001 Vol. 756:327-335).

Claim 21 is drawn to a method for producing a transgenic peanut plant with reduced or undetectable allergen protein content in the seed, comprising identifying a homologous region common to more than one *Ara h* allergen gene; cloning the homologous region in a vector modified for peanut transformation; transforming a recipient peanut plant cell with the vector; and identifying a transgenic plant that produces seeds having reduced or undetectable allergen protein content.

Tada et al. teach a cloned gene encoding the 16-dKa allergenic protein from rice was operably linked to a promoter, cloned in a vector and transformed by electroporation in rice seeds (see page 341, second column). Tada et al. further teach the level of the 16-kDa protein was significantly reduced in the rice seed in a number of the progeny, however, the protein was not completely eliminated in these plants (see Figures 3 and 4). Tada et al. finally teach that this approach could be used in other crops containing known allergens, such as peanuts and soybeans, to selectively reduce or eliminate the levels of specific allergenic proteins (see page 181, last paragraph).

Tada et al. do not teach identifying a homologous region common to more than one *Ara h* allergen gene.

Kleber-Janke et al. teach the alignment of the deduced amino acid sequences of *Ara h*2, h6, and h7 shows the identical regions of these three members (see Figure 3).

It would have been obvious to one of ordinary skill in the art to devise a method for producing a transgenic peanut plant with reduced or undetectable allergen protein content in the seed since Tada et al. taught the production of transgenic rice plants with a reduced 16-kDa allergen protein in the seed.

One of ordinary skill would have been motivated to substitute the transgenic rice plant with a transgenic peanut plant since Tada et al. taught the approach could be used on other crops such as peanuts. One of ordinary skill in the art would have been motivated to substitute the 16-kDa allergen protein with an *Ara h* allergen gene because the art taught that both genes are major dietary allergens in rice grain and peanut grain, respectively (Shewry et al.).

It would have been obvious to one of ordinary skill in the art to identify a homologous region common to more than one *Ara h* allergen gene because Kleber-Janke et al. taught the identity of similarities between allergens can determine the frequency recognition of IgE serum binding in peanut-sensitive patients. One of ordinary skill in the art would have expected to be successful in identifying a homologous region common to more than one *Ara h* allergen gene since the prior art explicitly taught such techniques by aligning the deduced amino acid sequences (Kleber-Janke et al.). It would have been obvious to one of ordinary skill in the art to identify the homologous region, link it to a promoter and clone it into a vector since Shewry et al. taught such methods could silence endogenous genes in plants. One of ordinary skill in the

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art would have expected to be successful in cloning the promoter-linked homologous region in a vector and transforming a cell with that vector since Tada et al. taught such methods would successfully reduce allergen protein content in seeds.

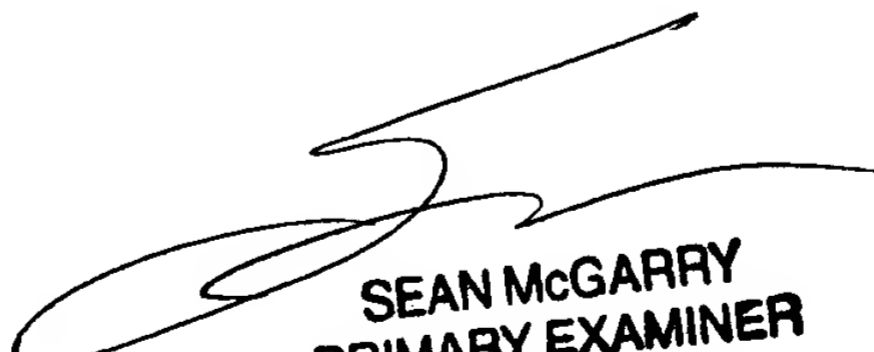
The invention as a whole would therefore have been obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
October 30, 2002


SEAN MCGARRY
PRIMARY EXAMINER
1635